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ATROPINE, SCOPOLAMINE, AND DITRAN: COMPARATIVE PHARMACOLOGY AND ANTAGONISTS IN MAN

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Edgewood Arsenal
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by

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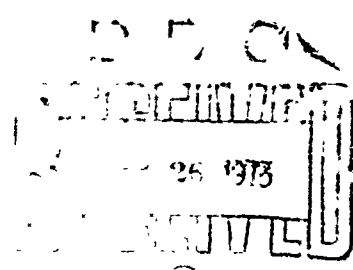Arthur H. Hayes, Jr., M.D.

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Atropine, scopolamine, and Ditran, three centrally active anticholinergic compounds, were administered to 158 normal young men in a dose range broader than any previously reported in order for us to study serially their central and peripheral effects. The findings indicate that there are no qualitative differences in the actions of these compounds, but that there are differences in potency, in relative central affinity, and in time course of effects. The toxic effects of belladonna-related substances respond well to certain anticholinesterase substances, such as physostigmine, sarin, and tetrahydroaminoacridine (THA), but not to others [neostigmine and diisopropyl phosphorofluoridate (DFP)], nor do they respond to the unrelated drug methylphenidate nor to the phenothiazines. The hallucinations, confusion, and incoherence produced by high doses of anticholinergic compounds seem best classified as simple delirium, rather than as "psychotomimetic" or "psychedelic" syndromes.

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FOREWORD

The work described in this report was authorized under Task 1W062116AD2103, Medical Effects of Chemical Agents, -03 Clinical Evaluation of Chemical Agents. This work was started in June 1964 and completed in December 1969.

The volunteers in these tests are enlisted US Army personnel. These tests are governed by the principles, policies, and rules for medical volunteers as established in AR 70-25 and the Declaration of Helsinki.

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DIGEST

Atropine, scopolamine, and Ditran, three centrally active anticholinergic compounds, were administered to 158 normal young men in a dose range broader than any previously reported in order for us to study serially their central and peripheral effects. The findings indicate that there are no qualitative differences in the actions of these compounds, but that there are differences in potency, in relative central affinity, and in time course of effects. The toxic effects of belladonna-related substances respond well to certain anticholinesterase substances, such as physostigmine, sarin, and tetrahydroaminoacridine (THA), but not to others [neostigmine and diisopropyl phosphorofluoridate (DFP)], nor do they respond to the unrelated drug methylphenidate nor to the phenothiazines. The hallucinations, confusion, and incoherence produced by high doses of anticholinergic compounds seem best classified as simple delirium, rather than as 'psychotomimetic" or "psychedelic" syndromes.

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ATROPINE, SCOPOLAMINE, AND DITRAN: COMPARATIVE PHARMACOLOGY AND ANTAGONISTS IN MAN

I. INTRODUCTION.

The human pharmacology of the atropine alkaloids and of related synthetic compounds has been the subject of many publications during the past century. Much of this information is from studies employing low doses, or from clinical reports of accidental or intentional poisoning. In particular, very little systematic information is available concerning the effects of these agents on higher integrative functions in human beings.

As a result, many areas of uncertainty and controversy persist. For example, not all investigators agree that atropine, scopolamine, and their synthetic congeners such as Ditran (JB-329)* are pharmacologically similar, or that they all achieve their effects on behavior through anticholinergic mechanisms. Nor is there unanimity concerning the effectiveness of various cholinergic substances such as neostigmine and physostigmine in reversing the central toxicity of these compounds. No consensus exists concerning the classification of the behavioral syndrome observed with these compounds. Even the descriptions of signs and symptoms provided by various authors are so disparate as to be, at times, contradictory.

In a review of the behavioral and encephalographic effects of atropine and related compounds, Longo[1] observed that "a comparison of the central effects of atropine and scopolamine over a wide range of dosage has not been undertaken in man; and therefore no real substantiation of a qualitative difference on the central nervous system is yet available." This report presents data relevant to some of these points.

II. METHODS.

The subjects, 149 normal US Army enlisted men, averaged 23 years of age, 74 kg of body weight, 12 years of formal schooling, and a score of 117 on the Army GT test. All subjects, having undergone comprehensive medical, psychological, and clinical laboratory evaluations, were in excellent health.

The subjects, volunteering freely for the experiments, received no special rewards for their services. They were told that the purpose of the test was to measure the effect of a chemical substance upon their ability to perform physically and mentally. If an antidote were to be tested, the subjects were also informed Although the general properties of the drugs were explained, the expected effects were not described in detail. Instead, the physician reviewed the results with the volunteers after the test was completed.

The subjects were tested in a specially designed, cushioned, air-conditioned ward area with separate cubicles for each individual; a larger communal area was used for eating and for recreation. The men became familiar with this environment and with the ward personnel during a period of several days prior to receiving the agent in which physiological and psychological performance baselines were recorded. They slept in their cubicles the night before the test and ate a light breakfast at about 0700; the agent was administered about 2 hours later. Each man was

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* Ditran is a mixture of N-ethyl-2-pyrrolidyl-methyl-cyclopentylp' .iyl glycolate (70%) and N-ethyl-3-piperidyl-cyclopentylphenyl glycolate (30%).

[1] Longo, V. G. Behavioral and Electroencephalographic Effects of Atropine and Related Compounds. Pharmacol. Rev. 18, 965-966 (1966).

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observed for at least 24 hours after dosing. When not undergoing scheduled measurements, the men were allowed to eat, sleep, read, converse, play cards, or watch TV as they wished.

Physiological measures, including heart rate, blood pressure, axillary temperature, and respiratory rate, were obtained by standard clinical techniques after the subject had rested for at least 2 minutes in the supine position. Pupil size was estimated by matching subject's pupil to one of a graded series of solid black circles along the edge of a circular card. A constant, moderately bright source of illumination was used. Cognitive performance was assessed by the Number Facility (NF) subtest of the Repetitive Psychometric Measures.[2] Each of the 20 equivalent forms of this subtest contained 90 addition problems composed of three 1- or 2-digit numbers (drawn at random). The score, based on the number of correct answers given in 3 minutes, was expressed as a percentage of the individual's previously established baseline. Corrective lenses or eye drops containing a cholinergic antagonist to restore nearly normal vision were used whenever visual difficulties seemed likely to affect the NF performance. Behavioral changes were quantified using a Behavior Checklist (BCL) which consisted of 24 items that were rated 0, 1, or 2 (absent, mild, or marked) at prescribed intervals. Verbal descriptions were entered in the clinical record at frequent intervals. Subjects wrote a personal account of their experiences and completed a 40-item Symptom Checklist (SCL) at the conclusion of the experiment.

Baseline physiological values were designated as the lowest, or the most typical (as appropriate) of 5 to 10 pretest observations distributed over a 2- to 3-day period. Number Facility baselines were computed by averaging the five highest of 20 practice trials distributed over the same period.

The drugs, doses, routes of administration, and antagonist substances employed in the various test series are listed in table A-I. Intramuscular injections were given in the deltoid muscle; but divided sites were used if injection volume exceeded 2 ml. Saline controls were used in treatment studies, but not in dose-response studies of individual drugs, where differential effectiveness of various doses was the question of primary interest. In all cases, however, neither the subject nor the personnel recording the observations and measurements knew the dose given.

III. RESULTS.

A.   Clinical Description of Effects.

1.   General.

Clinically, the responses to atropine, scopolamine, and Ditran were virtually identical, consisting of signs of peripheral parasympathetic blockade and a diffuse impairment of central nervous system (CNS) function. Intensity of response varied predictably with the dose, but scopolamine was the most potent centrally, Ditran was the least potent peripherally, and atropine was the slowest in onset and the longest in duration.

The sequence of effects at the high doses of each drug could be divided roughly into three phases. In the first, peripheral autonomic effects such as tachycardia and dryness of the mouth were most conspicuous. Overlapping this was a second phase characterized by

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[2] Moran, L. J., and Mefferd, R. B. Repetitive Psychometric Measures. Psychol. Rep. 5, 269-275 (1959).

* Tables A-I through A-VI are in appendix A.

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neurovegetative disturbances of central origin such as somnolence, restlessness, ataxia, incoordination, hyperreflexia, hyperthermia, and hypertension. A third phase, overlapping the second, was marked by disruption of awareness and the loss of ability to pay attention, to carry out instructions, to speak coherently, or to interpret stimuli realistically. These effects persisted even when those associated with the first two phases had disappeared; typically, these effects lasted 6 to 8 hours for Ditran and scopolamine and 10 to 12 hours for atropine.

Because of the complex and dramatic character of the CNS effects, they are described in detail below. Quantitative aspects of the behavioral and physiological changes are presented in subsequent sections.

2. Central Nervous System (CNS) Effects.

a. Level of Consciousness.

Drowsiness, progressing within 30 to 60 minutes to somnolence, stupor, or even semicoma, was produced by all three drugs. Restlessness, with much shifting about of the lower extremities, was often superimposed upon this depression of consciousness. Later the opposite seemed to apply in the more severely affected cases, with suppression of sleep and hyperactivity taking the place of early sedation.

At the more intense end of the response scale, subjects progressed from the early stupor or semicoma into a "pseudowakeful" state, in which their eyes were open and they stared at, and feebly manipulated, portions of their clothing, the bed coverings, or phantom objects such as invisible drinking glasses or cigarettes. Momentary attention could be gained by calling the subject's name sharply or asking him a sudden question, but the answers were very unpredictable and often left the impression that the subject was in a "world of his own," or "daydreaming," in a bewildering, disconnected, incomprehensible manner.

b. Mood and Affect.

During the preliminary phase of restlessness and diminishing alertness, many subjects were apprehensive and irritable. Some said they did not "feel good," but could not elaborate. A few, on the other hand, seemed to become euphoric, said they felt "high," and giggled at their increasing ineptitude.

Once past this "induction" period, there was a further decrease in activity during the period of somnolence or stupor. Activity then progressively increased during the ensuing pseudowakeful state, but at this time behavior was thoroughly disorganized and at times seemed random and purposeless. In spite of their confusion, however, most subjects were curiously docile and tractable during this period.

Later on, suspiciousness, fear, and negativism occasionally appeared as the subjects began to piece together, but in a faulty manner, the situation in which they found themselves. Systematized paranoid delusions did not develop in these subjects, but it sometimes appeared that they might have if recovery had not proceeded so rapidly.

c.   Intellectual Functions.

   (1)   Memory.

   A variable degree of impairment, greatest for recent events, was evident in subjects receiving high doses. Whenever the subject's speech and attention span were sufficiently intact to permit questioning, remote memory seemed virtually intact, but a considerable deficit for experiences of the previous few hours was present. Immediate and slightly delayed recall was most strikingly impaired, and many subjects could not repeat even short sentences, or number sequences. Often they reported being unable to remember what they themselves had said only a moment before. Following recovery, amnesia was observed for the period during which gross confusion had been evident, although isolated events could be recalled for a while, in a manner analogous to the transient ability to recollect dreams on awakening. Even when recovery was "abrupt," however, as in the case of subjects receiving treatment, very little could be remembered.

   (2)   General Information.

   In keeping with the relative sparing of remote memory, the ability to answer factual questions on subjects of common knowledge was not greatly disturbed. The subjects' difficulties in grasp and attention, however, often made evaluation difficult. One subject, for example, easily replied, "Shakespeare," when asked, "Who wrote Hamlet?" but seemed unable to answer the same question 5 minutes later.

   (3)   Calculation.

   The same variability in performance was encountered in the approach to simple mathematical problems. Serial subtraction of 7's, for example, was often disrupted by the time the third or the fourth number was reached, as the subject drifted off into unrelated mutterings. Rarely could he return to the original problem once his train of thought was diverted in this way! Particular difficulty was noted with units of measurement: a request to calculate the area of a 3- by 4-foot rectangle elicited the answer "12 days."

   (4)   Abstraction.

   Subjects displayed considerable confusion in explaining proverbs and in identifying word similarities and differences. A tendency to be overly concrete and literal, common to many organic disturbances, was observed. Again, however, evaluation was often difficult because of the overlay of distractability and poor enunciation.

   (5)   Judgment.

   In much of their spontaneous behavior, the subjects gave evidence that their judgment, in the sense of a capacity to modulate one's responses in accordance with prevailing physical and social realities, was grossly altered. Faulty social judgment, for example, was demonstrated by the subjects' uninhibited use of profanity and vulgar speech while conversing with the nurse or the physician.

   Failure to distinguish between objects and persons was also evident. One subject attempted to take a casual bite from the doctor's forearm, while another apologised to the drinking

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fountain when he bumped against it. Bizarre and absurd acts sometimes occurred. One man tried to write his name on a piece of chicken with a ball-point pen, and another tried to leave the room through the medicine cabinet. Many subjects seemed to have difficulty making use of available cues when answering questions. When asked whether it was night or day, for example, one replied, "Night-time," even though he could see daylight through a nearby window.

d. Perception.

Subjects in the pseudowakeful state appeared to experience illusions arising from objects in the room, as well as hallucinations which could not be traced to any specific stimulus. Vague shadows were frequently perceived as large animals; slender shapes were "snakes." A hassock might become a pig; a strip of moulding would be transformed into the white line down a highway or the fat in a strip of bacon. Faces of family or friends appeared on the wall or materialized in empty air, and subjects would converse casually with these apparitions. In contrast to the kaleidoscopic, surrealistic visions associated with LSD intoxication, the hallucinations of atropine delirium were pictorial and realistic, involving ordinary scenes and objects.

As recovery progressed, the size and complexity of these fancied images diminished; bears and alligators were replaced by rats and mice, then spiders, and finally ants, which resolved, ultimately, to specks on the floor. Another interesting perceptual change that occurred with great regularity was the illusion of red (sometimes yellow) skin—not only the subject's own, but everyone else's as well. One man tried to wash this off, thinking it was blood.

Hallucinations were sometimes panoramic: a "baseball game" was in progress on the floor of one subject's cubicle, and a "DC-3 (or possibly a DC-4)" touched down neatly on another's. A third man described a battle from the Civil War which was being enacted on his wall by armies of men in full regalia. The Lilliputian character of many of the hallucinations permitted a great deal to happen in a small space.

Although most of the reported illusions and hallucinations were visual, auditory and tactile misperceptions were occasionally noted. Olfactory illusions were rarely reported.

e. Time Sense and Orientation.

A disturbance in the perception of time was the most common abnormality of the sensorium. In mild cases, this was nothing more than a feeling that time had slipped away, or flown, during the few hours of the drug's maximal effects. In more severe intoxications, however, subjects sometimes lost track of the day of the week, or even of the month and year. Such individuals often spoke as if they were at home or at their regular duty stations. They might address the physician as if he were an old friend or an acquaintance from their homes.

Disorientation, as such, was inconstant, and never took the form of an *idee fixe*; a patternless mixture of correct and erroneous statements might be a better description, and even the most confused subjects had fleeting moments of lucidity. This paradoxical occurence of a coherent, highly appropriate response, in the midst of total confusion, appears to be a typical feature of delirious behavior.

f. Expression and Comprehension.

The mechanisms governing phonation and other modalities of expression, such as writing and drawing, were affected in several ways. Slurred speech and deterioration in the quality

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of handwriting were early manifestations of toxicity. A less obvious change, seen later, was a loss of resonance and "melody" from the voice, rendering it monotonous, slightly higher in pitch, and devoid of inflection, somewhat reminiscent of the rote utterances of a mass or liturgy.

Even more impressive than these changes in quality, however, were the alterations in speech content. At the height of the intoxication, as subjects passed from stupor into pseudo-wakefulness, meaningless muttering (the so-called "mussitant delirium" of the older psychiatric literature) was characteristic. Speech content at this point was fragmentary and structureless. Gradually, as articulation improved, intelligible phrases or short sentences could be "made out." These were generally declaractive, "He's got a laundry ticket," or exclamatory, "Did you see that!" Clichés, profanity, and colloquialisms were predominant. Metaphors and figures of speech were interpreted literally. When asked, "What time is it?" one man replied, "What time is what?" It was generally impossible to find out what a subject had in mind when he made a nonsensical statement because he could rarely understand the question, remember what he had been thinking, or formulate a suitable answer. Only with short, simple questions permitting quick, semiautomatic replies could any meaningful interchange be achieved.

g. Insight.

A strong tendency to explain away cognitive difficulties, to "save face," as it were, was conspicuous throughout the period of intoxication. Excuses and alibis such as "I never was very good in arithmetic," were offered for the inability to do elementary mathematical calculations. At other times, subjects attempted to parry the questioner by asking him to repeat the question, or by inquiring innocently, "You mean you want me to do that right now?" If the examiner were too persistent, the subjects often became flustered and irritable, sometimes refusing to make further efforts. Many seemed genuinely unable to recognize their own defects and insisted that they were still fully capable. Some expressed indignation at being "treated like a little kid" and constantly being assisted with everything. even though their behavior was, in fact, more poorly organized than that of a small child. Paradoxically, when a subject began to realize that he was not functioning with full efficiency, it could be safely assumed that he was close to full recovery.

Insight concerning perceptual distortions was remarkably lacking, and most subjects were convinced that wnat they saw was really there, however improbable this might seem. Even when they recalled being given a drug earlier the same day, often it did not occur to them that these phenomena might in any way be attributable to the effects of the drug, a fact which illustrated a general inability of the subject to integrate readily available information.

h. Experimental Aspects.

Illustrative excerpts from the subjects' written reports and from the nurses' notes are presented in table A-II. Contrary to the prevalent notion that amnesia is an essential feature of delirium, many aspects of the experience can be remembered if recall is attempted immediately following recovery. Like dreams, however, the delirious experience is quickly forgotten unless the recollection process is undertaken promptly, as soon as possible after "awakening."

B. Quantitative Measures of Behavioral Effects.

1. Behavior Check List (BCL).

In analyzing dose-response relationships, the highest rating for each item on the BCL was used to represent the individual's score on that item. Probit analysis[3] was then used to compute

[3]Bliss, C. I. The Statistics of Bioassay. Academic Press, Inc., New York. 1952.

the value of the effective dose for 50% of the population (ED50) for each item at each of the two criterion levels, mild [1] and marked [2]. Tab'e A-III summarizes the ED50's which were considered meaningful (i.e., slope significantly greater than zero, and a value within the range of dosage actually studied).

The relative central potency of the three drugs was estimated by pairwise comparison of the ED50's for each behavioral item. Since the ratios thus obtained were found by t-test not to be significantly affected by the criterion used (mild versus marked), a single ratio was obtained by averaging, and the mean ratio for the entire list of items was taken as an overall index oi the relative central potency of the members of the pair. Using this method of comparison, scopolamine (intramuscular) was more potent than atropine by a factor of 7.5, and Ditran was more potent than atropine by a factor of 1.3.

2. Symptom Check List (SCL).

A similar analysis was carried out for the SCL. Since data were available only for the 12 and 17 μg/kg groups of intramuscular scopolamine, interpolation was used to obtain a response percentage for each item which could be substituted into the corresponding probit equation for atropine. Ratios derived in this manner are presented in table A-IV. Thus, based on the subjects' estimates, scopolamine is 8.8 times as potent as atropine. Symptom Check List data for Ditran were insufficient for analysis.

3. Number Facility (NF).

Tne use of the NF test as the principal objective measure of cognitive performance was based on earlier studies with related agents in which it was found that the drug effects tended to be highly correlated across a variety of performance measures. The NF results may therefore be taken as indicative of overall intellectual efficiency at the time of testing. Figures B-1 and B-2 summarize graphically the relationship between dose, experimental time, and NF score for the three drugs. Considerable regularity is evident in the response curves, both in time course and in proportionality of peak intensity to dosage.

From a tabulation of clinical effects associated with various levels of NF performance, it was observed that hallucinations, disorientation, and incoherence consistently appeared whenever NF scores fell below 10% of the baseline. The dose necessary to produce a decline in NF to below 10% in half the population (ED50) was calculated by probit analysis[3] to be 152 μg/kg, 20 μg/kg, and 100 μg/kg for atropine, scopolamine, and Ditran respectively.

By regression techniques, the times at which an average individual receiving such doses would fall below, and return from, selected performance levels (e.g., 25% and 50%, representing marked and moderate impairment) can be estimated, as in figure B-3.

Relative central potency of the three compounds based on NF scores is summarized and compared with estimates based on the BCL and the SCL in table A-V.

C. Quantitative Measures of Physiological Effects.

Heart rate was significantly affected by all thv compounds studied. Representative data illustrating time course and dose-response relationships are shown in figures B-4 and B-5. Heart rate

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*Figures B-1 through B-13 are in appendix B.

changes appeared earlier and subsided sooner than the changes in NF score shown above. Also, at the low doses of scopolamine and Ditran, bradycardia was observed after a brief period of modest tachycardia. The probability that this brad-cardia, which is maximal about the same time as the peak decrement in NF score, is of central origin was supported by the observation that methylscopolamine, a quaternary analog of scopolamine which is largely excluded from the brain by its low lipid solubility, produced only tachycardia, even at the lowest doses.

Blood pressure changes, both systolic and diastolic, paralleled in direction and time course those described for heart rate. At the highest doses of atropine, elevations in mean blood pressure of as much as 60 mm Hg were seen. The peak elevations were generally intermediate in time of occurrence between the peaks for heart rate and NF changes, suggesting a central component, but one which appears earlier than that which produces the cognitive effects.

Respiratory rate did not display any consistent alteration with any of the drugs tested. Axillary temperature showed a rise of 1° to 2°F at the high doses of all three drugs, but this was considerably influenced by room temperature, which varied by 10°F, and did not lend itself to statistical analysis.

Pupil size was definitely increased by the three agents, and some relationship to dosage was discernible (data not shown). The peak effect was later than the peak effect on the performance test, suggesting a delay in penetration of the drug to the site of action and the presence of a central component in the mydriatic action, in addition to a direct effect on the iris muscle.

Distinct differences were observed among the compounds studied in their relative strength of action upon peripheral and central mechanisms (as measured by heart rate increase and NF score, respectively). To provide a comparison of "central/peripheral (C/P) potency ratios," ED50's were calculated for heart rate increase of 30 bpm and divided by the ED50's for lowering NF to 10% of baseline (a 90% decrement). For methylscopolamine, doses sufficient to produce marked central effects were not administered, so the same comparisons were made using the ED50's to produce a lowering of the NF to 75% (a 25% decrement). For each compound, the ratio of the ED50 for a 25% decrement to the ED50 for a 90% decrement might be considered a steepness index of potency for that compound. These, along with the other ratios, are given in table A-VI. Scopolamine (intramuscular) causes the least, and atropine and methylscopolamine produce the most peripheral effects to obtain the same amount of central activity. On the other hand, for a given increment in dose, Ditran and scopolamine (intravenous) produce a greater decrement in performance.

D.   Treatment Studies.

1.   Physostigmine.

Figure B-6 shows the effectiveness of a single 60-μg/kg intramuscular dose of physostigmine salicylate given 2 hours after atropine sulfate (175 μg/kg, im). Within 15 minutes, dramatic clinical improvement was evident, subject's alertness was restored as well as his ability to respond coherently to questions. Within 4 hours, the effects of treatment had dissipated and subjects reverted to the untreated level.

In figure B-6, it can also be seen that similar treatment with neostigmine produced a dramatic reduction in heart rate, but did not affect NF scores. This is attributed to neostigmine's

quaternary structure, which reduces its lipid solubility, and hence its penetration of the blood-brain barrier. (The greater reduction in heart rate achieved by neostigmine may represent an "unmasking" of the central slowing action of atropine via vagal disinhibition.)

There is an increased therapeutic effect of physostigmine with increasing doses in the range of 15 to 50 μg/kg (figure B-7). Subsequent experience has shown that a dose of 50 to 60 μg/kg (im) is optimal. A previous report[4] indicated a relative refractiveness to this antidote early in the time course of scopolamine intoxication, as there was a minimal therapeutic effect when the drug was administered at 15 minutes and a suboptimal beneficial response when it was given at 30 minutes. The relative refractiveness to early treatment is unexplained at this time.

Ditran intoxication responded in a similar manner to physostigmine (figure B-8). Again, the therapeutic benefit was less when the antidote was given earlier. Physostigmine caused almost complete subsidence of the signs and symptoms of delirium.

Despite its effectiveness in reversing the cognitive impairment and tachycardia, a single dose of physostigmine was not effective in reversing the decreased accommodation caused by these anticholinergics. However, in other investigations we have found that repeated doses of physostigmine, such as may be used to treat intoxication with a massive dose of one of these substances or to treat intoxication caused by an anticholinergic substance with a long duration of action, do cause some reversal of the visual impairment. This may be due to the relatively slow penetrance of physostigmine into the aqueous humor or to other factors not well understood.

2. Diisopropyl Phosphorofluoridate (DFP).

Diisopropyl phosphorofluoridate was administered to four subjects with slight benefit, as shown in figure B-9. The fact that DFP is a preferential inhibitor of pseudocholinesterase and did not lower true cholinesterase more than minimally may explain its relative ineffectiveness. Sarin (isopropyl methylphosphonofluoridate), on the other hand, was very effective (figure B-10) even though it caused only a moderate inhibition of pseudocholinesterase, but did inhibit true ChE.

3. Tetrahydroaminoacridine (THA).

Because of reports[5,6] that THA is able to reverse Ditran intoxication, we administered this compound to a few subjects. It was found to be quite effective against scopolamine (figure B-11), as well as Ditran (not shown). Tetrahydroaminoacridine is, among other things, a cholinesterase inhibitor, particularly active with respect to pseudocholinesterase. In this respect, its efficacy seems somewhat anomalous if true cholinesterase inhibition is indeed necessary to produce reversal of delirium. Since no information is available in these studies concerning the state of brain cholinesterase, it is not possible to resolve this interesting question without further investigation.

4. Miscellaneous Drugs.

Because tranquilizers might be used to quiet a delirious patient, the effects of two representative phenothiazine tranquilizers, chlorpromazine and perphenazine, were evaluated in

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[4]Crowell, E. G., Jr., and Ketchum, J. S. The Treatment of Scopolamine-Induced Delirium with Physostigmine. Clin. Pharmacol. Therap. 8, 409-414 (1967).

[5]Gershon, S. Blocking Effect of Tetrahydroaminacrin on a New Psychotomimetic Agent. Nature. 186, 1072-1073 (1960).

[6]Gershon, S., and Olariu, J. JB-329-a New Psychotomimetic. Its Antagonism by Tetrahydroaminacrin and Its Comparison with LSD, Mescaline and Scmyl. J. Neuropsychiat. 1, 283 (1960).

subjects who received scopolamine. Twenty-five milligrams of chlorpromazine caused moderate, and 50 mg caused marked, potentiation of the NF decrement produced by 8 μg/kg of scopolamine (figure B-12). Twenty-five milligrams of chlorpromazine caused a prolongation of the syndrome produced by 24 μg/kg of scopolamine, whether given at 45 or 150 minutes (figure B-13). Similar increases in, or prolongation of, effects were observed when 5 mg of perphenazine were administered to subjects who had received 8 or 24 μg/kg of scopolamine 45 minutes earlier (not shown).

To test the possibility that a central stimulant might reverse the depressant action of scopolamine, methylphenidate was given together with small doses of scopolamine. Although methylphenidate alone produced a small temporary enhancement of NF performance, it did not reverse even the mild decrement caused by 8 μg/kg of scopolamine (not shown).

IV. DISCUSSION.

From the results obtained, it would appear that the pharmacological effects of atropine, scopolamine, and Ditran are essentially similar in their effects in man. Previously made distinctions disappear when comparisons are made among doses of equal relative magnitude.

In particular, it is clearly evident that peripheral effectiveness, represented by the ability to increase heart rate, and central effectiveness, measured by the ability to lower NF performance, are not highly correlated. Thus, scopolamine has a preferential central action which is approximately eight times that of atropine, and six times that of Ditran. These ratios are not appreciably different when the BCL is used to estimate central effectiveness even though individual BCL items vary somewhat in this regard. Likewise, the SCL, which encompasses a broader range of effects, indicates that scopolamine is, on the average, close to nine times as potent as atropine. One must conclude that the central actions of the three agents are nearly identical when allowances are made for the differences in central potency.

In these studies, the NF test was heavily relied upon as a measure of central effect. The justification for this is twofold: First, previous experience with a variety of performance measures, including several designed to assess particular cognitive or psychomotor skills, has convinced us that the effect of atropine-like substances on performance is similar, regardless of the measure employed. This is in keeping with the observation that the central effects of these compounds are apparently quite diffuse, rather than selective. Secondly, the clinical picture was found to bear a close relationship to the level of performance on the NF test. Whenever NF scores fell below 10% of the baseline, clinical evidence of delirium was invariably present.

Analysis of the time course suggests that three phases of drug activity can be distinguished. In the first of these, peripheral parasympatholytic effects such as tachycardia reach their maximum values. A second phase, overlapping the first, is characterized by disturbances of central physiological motor/regulatory systems, manifested by drowsiness, restlessness, hyperreflexia, incoordination, ataxia, dizziness, nausea, bradycardia, hypertension, and hyperthermia. The third phase, overlapping the first two, consists of a diffuse disturbance of the higher integrative systems of the forebrain; its features include impairment of attention, memory, perception, cognition, and expression

Since these phases can be distinguished with all three of the drugs studied, it is tempting to suppose that the receptor site configurations may be distinctive for the three constellations of effects described above. An alternative explanation would be to assume that the accessibility of these sites is different.

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The terms used in published accounts to describe the behavioral syndrome produced by large doses of these drugs vary considerably, including "psychotomimetic" and even "psychedelic." The most accurate designation is delirium, an ancient but useful term implying restlessness, confused speech, and hallucinations. In an excellent monograph, Wolff and Curran[7] made the point that delirium is a clearly definable psychiatric entity with diverse etiology. Its dominant feature is moment-to-moment variability. "Defects in grasp, failure in sustained mentation, fear or anxious suspicion, misinterpretation, hallucinosis, and restlessness are its prevailing manifestations." Wolff found, in 108 cases, that these manifestations were surprisingly constant whether the causative agent was alcohol, bromides, lead encephalopathy, heart failure, uremia, or hypothyroidism.

Engel and Romano[8] proposed that delirium be viewed as a "syndrome of cerebral insufficiency," analogous to cardiac or renal failure, where the result may be appreciated even when the exact cause is not known. While endorsing this useful notion, we are less in accord with the authors' proposal that the diagnosis be made only when correlated changes in the EEG (a characteristic type of slowing) are observed. Although such changes may indeed be seen regularly, delirium can be diagnosed quite reliably on clinical grounds alone. The specific etiology, furthermore, depends for its identification upon clinical acumen and sometimes upon chemical tests, but rarely upon the EEG. While it is reasonable to hope that we may some day differentiate subgroups of delirium associated with various classes of causative agents, until then delirium must remain a well-defined, although nonspecific, response to a wide spectrum of noxious conditions.

Conversely, while atropine, scopolamine, and Ditran have been shown in these experiments to produce the same clinical syndrome of delirium, one is not entitled to conclude from this that the mechanism is identical in all three. Neither, however, can we agree with Gershon and Olariu,[6] Abood,[9] and others that Ditran is pharmacologically distinctive from the other two. We found neither the differences in clinical psychiatric effects nor the differences in response to antagonist substances reported by these authors. All three drugs produced the classical signs of muscarinic blockade at peripheral sites. All produced delirium which was reversible by appropriate cholinergic therapy, implying that the central actions were attributable to central cholinergic blockade. There does not seem to be any compelling reason at present to regard these compounds as fundamentally different in their mechanisms of action.

In retrospect, it is possible to understand how previous workers might have reached different conclusions on this point. In some instances, the effects of Ditran were not classified as simple delirium, perhaps because of a paucity of comparative experience with atropine and scopolamine. The hypothesis that Ditran acted otherwise than through cholinergic blockade was supported by the failure of workers such as Lang[10] to antagonize Ditran intoxication in dogs with 40 μg/kg of physostigmine. This dose, however, was undoubtedly too small. White[11] and Carlton[12] who gave 0.4 mg/kg of physostigmine to rabbits 15 minutes after 0.5 mg/kg of Ditran and did not observe EEG reversal to normal, may have given treatment too early. As noted earlier, the relative ineffectiveness of early physostigmine treatment has been reported by Crowell and Ketchum.[4]

[7] Wolff, H. G., and Curran, D. Nature of Delirium and Allied States: Dysergastic Reaction. Arch. Neurol. Psychiat. 33, 1175-1215 (1935).

[8] Engel, G. L., and Romano, J. Delirium, a Syndrome of Cerebral Insufficiency. J. Chron. Dis. 9, 260-277 (1959).

[9] Abood, L. G. A Psychosis-Producing Drug As A Tool in Studying Nerve Excitation. Recent Advances Biol. Psychiat. 8, 119-125 (1965).

[10] Lang, W. et al. Some Antagonists of Atropine-like Psychotomimetics. J. Pharm. Pharmacol. 15, 831-840 (1963).

[11] White, R. P. Electrographic and Behavioral Signs of Anticholinergic Activity. Recent Advances Biol. Psychiat. 8, 127-137 (1965).

[12] Carlton, P. L. Cholinergic Mechanisms in the Control of Behavior by the Brain. Psychol. Rev. 70, 19-39 (1963).

It is curious, and historically interesting, that physostigmine's ability to reverse atropine delirium has gone largely unrecognized by practicing physicians for so many years. Forrer and Miller[13] appear to be the first clinicians in this century to report unequivocal central antagonism in man between these two agents. Although few current pharmacology texts reflect this information, belated confirmations of physostigmine's value have recently begun to appear.[14,15] Animal pharmacologists, on the other hand, appear to have appreciated the mutual antagonism between physostigmine and the belladonna alkaloids for many years.[16-18]

An ironic footnote to this peculiar oversight concerning physostigmine was our discovery (while reviewing the literature) of an article[19] published in Germany in 1864 in which the dramatic efficacy of physostigmine (administered orally as extract of calabar bean) in the treatment of atropine delirium was clearly documented. In discussing the results, the author commented: "I do not believe that the effects are to be credited to chance; the results appeared too quickly and too clearly to have made it possible to misunderstand the casual relationship. In order to determine the facts of this case objectively, it would be important in any event to conduct numerous and exact tests with calabar as an antidote to atropine." This prudent recommendation appears to have been given little heed by later workers in spite of the fact that atropine poisoning continued to claim an average of about 10 lives a year in England alone during most of the 19th century.

The results of our studies involving various phenothiazines in combination with scopolamine confirm the findings of other workers who have studied such combinations in animals.[20] The use of phenothiazines in the management of behavioral hyperactivity in cases of belladonna delirium, although advocated,[21] would appear ill-founded. Although motor activity may be reduced, overall brain function is still further compromised by such "treatment." The findings of other workers[11,12] that stimulants increase activity without lessening confusion, as well as our own limited results with methylphenidate, indicate that little benefit should be expected from the use of such compounds. Treatment with physostigmine, carefully regulated by the use of small, frequently repeated doses, provides a highly satisfactory method of counteracting the toxic effects of atropine and its congeners. No other drugs are required, and in our experience treatment may safely be continued with gradual reduction in dosage until all evidence underlying intoxication has subsided.

13 Forrer, G. R., and Miller, J. J. Atropine Coma; a Somatic Therapy in Psychiatry. Amer. J. Psychiat. 115, 455 (1953).

14 Duvoisin, R. C., and Katz, R. Reversal of Central Anticholinergic Syndrome. J.A.M.A. 206, 1963 (1968).

15 Gadecki, W. Reversal of Atropine Coma with Physostigmine. Psychiatrica Polska. 17, 587-589 (1967).

16 Bradley, P. B., and Key, B. J. The Effects of Drugs on Arousal Responses Produced by Electrical Stimulation of the Reticular Formation of the Brain. Electroenceph. Clin. Neurophysiol. 10, 97-110 (1958).

17 Funderburk, W. H., and Case, T. Effect of Parasy·athetic Drugs on the Conditioned Response. J. Neurophysiology. 10, 179-187 (1947).

18 Miller, F. R., Stavraky, G. W., and Woonton, G. A. Effect of Eserine, Acetylcholine and Atropine on the Electrocorticogram. J. Neurophysiol. 3, 131-138 (1940).

19 Kleinwachter, I. Observations Concerning the Effectiveness of Extract of Calabar Against Atropine Poisoning. Berliner Klinische Wochenschrift. 1, 369-377 (1864).

20 White, R. P., and Westerbeke, E. J. Differences in Central Anticholinergic Actions of Phenothiazine Derivatives. Exp. Neurol. 4, 317-329 (1961).

21 Atropine Sulfate, USP (Injection). Side Effects and Toxicity. Literature revised January 18, 1965, by Eli Lilly and Co. Indianapolis.

V. CONCLUSIONS.

1. Atropine, scopolamine, and Ditran (JB-329) produce qualitatively similar effects in normal volunteers when allowances are made for differential, central, and peripheral potency.

2. Intramuscular doses of 175-, 24-, and 150-μg/kg of atropine, scopolamine, and Ditran, respectively, produce in man the syndrome of delirium, a clearly-defined, nonspecific, psychiatric entity characterized by restlessness, confused speech, hallucinations, and moment-to-moment variability.

3. Clinically, and by objective measurement, all three drugs show a characteristic triphasic time course of action, consisting of peripheral parasympatholytic effects, disturbances of basic neuroregulatory functions, and disruption of higher integrative functions.

4. Physostigmine and certain other lipid-soluble cholinergic substances are highly effective in reversing the physiological and behavioral toxicity of all three drugs Phenothiazines, on the other hand, potentiate the impairment of cognitive function and would appear to offer little benefit.

LITERATURE CITED

1. Longo, V. G. Behavioral and Electroencephalographic Effects of Atropine and Related Compounds. Pharmacol. Rev. 18, 965-966 (1966).

2. Moran, L. J., and Mefferd, R. B. Repetitive Psychometric Measures. Psychol. Rep. 5, 269-275 (1959).

3. Bliss, C. I. The Statistics of Bioassay. Academic Press, Inc., New York, New York 1952.

4. Crowell, E. G., Jr., and Ketchum, J. S. The Treatment of Scopolamine-Induced Delirium with Physostigmine. Clin. Pharmacol. Therap. 8, 409-414 (1967).

5. Gershon, S. Blocking Effect of Tetraphydroaminacrin on a New Psychotomimetic Agent. Nature. 186, 1072-1073 (1960).

6. Gershon, S., and Olariu, J. JB-329-a New Psychotomimetic. Its Antagonism by Tetrahydroaminacrin and Its Comparison with LSD, Mescaline and Sernyl. J. Neuropsychiat. 1, 283 (1960).

7. Wolff, H. G., and Curran, D. Nature of Delirium and Allied States: Dysergastic Reaction. Arch. Neurol. Psychiat. 33, 1175-1215 (1935).

8. Engel, G. L., and Romano, J. Delirium, a Syndrome of Cerebral Insufficiency. J. Chron. Dis. 9, 260-277 (1959).

9. Abood, L. G. A Psychosis-Producing Drug As a Tool in Studying Nerve Excitation. Recent Advances Biol. Psychiat. 8, 119-125 (1965).

10. Lang, W. et al. Some Antagonists of Atropine-like Psychotomimetics. J. Pharm. Pharmacol. 15, 831-840 (1963).

11. White, R. P. Electrographic and Behavioral Signs of Anticholinergic Activity. Recent Advances Biol. Psychiat. 8, 127-137 (1965).

12. Carlton, P. L. Cholinergic Mechanisms in the Control of Behavior by the Brain. Psychol. Rev. 70, 19-39 (1963).

13. Forrer, G. R., and Miller, J. J. Atropine Coma; a Somatic Therapy in Psychiatry. Amer. J. Psychiat. 115, 455 (1958).

14. Duvoisin, R. C., and Katz, R. Reversal of Central Anticholinergic Syndrome. J.A.M.A. 206, 1963 (1968).

15. Gadecki, W. Reversal of Atropine Coma with Psysostigmine. Psychiatrica Polaska. 17, 587-589 (1967).

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16.   Bradley, P. B., and Key, B. J. The Effects of Drugs on Arousal Responses Produced by Electrical Stimulation of the Reticular Formation of the Brain. Electroenceph. Clin. Neurophysiol. 10, 97-110 (1958).

17.   Funderburk, W. H., and Case, T. Effect of Parasympathetic Drugs on the Conditioned Response. J. Neurophysiology. 10, 179-187 (1947).

18.   Miller, F. R., Stavraky, G. W., and Woonton, G. A. Effect of Eserine, Acetylcholine and Atropine on the Electrocorticogram. J. Neurophysiol. 3, 131-138 (1940).

19.   Kleinwachter, I. Observations Concerning the Effectiveness of Extract of Calabar Against Atropine Poisoning. Berliner Klinische Wochenschrift. 1, 369-377 (1864).

20.   White, R. P., and Westerbeke, E. J. Differences in Central Anticholinergic Actions of Phenothiazine Derivatives. Exp. Neurol. 4, 317-329 (1961).

21.   Atropine Sulfate, USP (Injection). Side Effects and Toxicity. Literature Revised January 18, 1965, by Eli Lilly and Co. Indianapolis.

APPENDIXES

TABLES

Table A-1. Summary of Subjects, Drugs, and Doses

Atropine Sulfate (intramuscular)			Scopolamine Hydrobromide (intravenous)			Scopolamine Hydrobromide (intramuscular)			Scopolamine Methylbromide (intramuscular)			Ditran (intramuscular)		
Dose	Treatment drug	No. of Subjects	Dose	Treatment drug	No. of Subjects	Dose	Treatment drug	No. of Subjects	Dose	Treatment drug	No. of Subjects	Dose	Treatment drug	No. of Subjects
µg/kg			µg/kg			µg/kg			µg/kg			µg/kg		
32		4	5	Methylphenidate	2	5		4	5		2	50		1
50		4	6		2	8		6	10		2	75		1
75		8	12		2	8	Perphenazine	3	15		3	100		2
125	Saline	6	15		3	8	Chlorpromazine	6	20		4	110	Physostigmine	6
175	Neostigmine	4	18		4	11		6	25		4	120	Physostigmine	3
175	Physostigmine	4	24		2	17		7	30		4	140	THA	2
175		4				20	THA	1				150		2
						24		13				150	THA	1
						24	DFP	4				150	Physostigmine	2
						24	Sarin	2				170		1
						24	Perphenazine	2				170	Physostigmine	1
						24	Chlorpromazine	4						
						24	THA	1						

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Table A-II. Descriptions by Subjects and Observers of the Effects of
Atropine, Scopolamine, and Ditran

Case No.	Dose	Time	Excerpt from clinical record
	µg/kg	hr	

Atropine Sulfate

Case No.	Dose	Time	Excerpt from clinical record
267	175	Post recovery	"There was a great need for me to laugh, yet I saw or heard nothing to laugh at."
203	175	Post recovery	"At times I saw big ants and small spiders. I turned red."

Scopolamine Hydrobromide

Case No.	Dose	Time	Excerpt from clinical record
563	12	0120	Talking to "people playing cards" at front of bed.
625	24	0230	Smoking imaginary cigarettes, sees "green bugs" crawling on walls and ceiling.
165	24	0545	Said a bumble bee bit him; then he ate it and it "tasted like coffee."
128	24	Post recovery	"I saw a man who was only 6 inches deep, 36 inches across the shoulders, and about 6 feet 4 inches tall. He was a sickly white, pin-pointed eyes, no eyebrows. . .had a knife and wanted to kill me."

Ditran

Case No.	Dose	Time	Excerpt from clinical record
145	160	Post recovery	"When I tried to draw on a cigarette, it was gone. My hands were bright red and the other subjects were red all over."
155	120	Post recovery	"I saw smoke on their clouds flying from head to foot on the ceiling above me. On the word tests, I was more occupied with getting the circle around a word. I didn't care how many words I got. I understood the math test, but I would often forget the total of a sum before I could record it. . . Twice I could not understand speech. Two doctors were saying "nothing." As hard as I could try, I could make no sense of what they said. . . I saw a western TV show, still I know I didn't; heard a radio show, which I know I didn't; and read a news article, which I know I didn't." "The feeling of incapacitation is anything but pleasant; I felt like a crippled tufted pheasant Which was lying in multicolored fuzzy grass In anticipation of being served under glass."

Table A-III. A Comparison of ED50's* for Selected Items: Behavior Check List

Sign	Atropine (intramuscular)	Atropine** Ditran (intramuscular)	Atropine** Scopolamine (intramuscular)	Atropine** Scopolamine (intravenous)
	μg/kg			
Restless and active	126.3/	1.2/	5.8/	7.8/
Cannot obey simple requests	135.0/	1.3/	6.4/	7.8/
Speaks without being spoken to	132.0/			5.6/
Hallucinating	169.0/	1.8/	8.0/	10.9/
Nonsense speech	142.0/		6.8/	
Short attention span	95.0/133.0	0.9/	7.9/6.7	/9.0
Confused—place	157.0/		6.8/	8.4/
Confused—time	130.0/173.0	1.3/	6.5/7.6	8.5/10.1
Confused—person	164.0/	1.7/	7.2/	10.2/
Impaired recent memory	130.0/173.0		11.2/7.7	/10.7
Tends to stumble	106.0/		8.8/	
Poor coordination	89.0/	0.9/	7.7/	7.1/
Mean by group		1.3/	7.6/7.3	8.3/9.9
Mean, both groups			7.5	8.7

* The figure on the left of the slash is for mild effects (scored as 1), and the figure on the right of the slash is for marked effects (scored as 2).

**Potency ratio (1/ED50 of atropine ÷ 1/ED50 of second drug).

Table A-IV. A Comparison of ED50's* for Selected Items: Symptom Check List

Sign	Atropine (intramuscular)	Atropine** Scopolamine (intramuscular)
	μg/kg	
Dreaming (hallucinations)	163.5/	11.0/
Food less appealing	125.1/	8.0/11.4
Always tired	43.2	2.5/
Did not feel good	94.6/	6.8/7.7
Dizzy	/95.0	6.5/8.2
Eyes blurry	/99.8	/10.3
Reflexes slowed	/148.2	12.9/10.6
Arms and legs weak	/138.2	9.6/10.4
Nauseated	146.1/	8.6/
Body felt as though it had been through workout	74.7/	5.8/3.1
Partial amnesia	163.5/	11.2/
Reached the point of drunkeness	/128.8	7.9/8.8
Floating on a cloud	168.2/	11.2/
Felt insecure	146.7/	8.0/
Hands cold	168.2/	10.7/
Nervous	102.0/	6.9/7.5
Double vision	146.1/	8.6/9.0
Restlessness		12.5/14.4
Mentally incoordinated		13.7/7.3
Thirsty all the time		4.8/10.6
Throat hurt when swallowing		7.2/10.6
Couldn't focus eyes		7.8/8.0
Uneasy		3.9/
Muscles twitched uncontrollably		9.2/7.9
Unorganized		7.7/
Lost sense of balance		9.7/9.5
Arms and legs red		8.2/
Felt irritable, impatient		9.1/
Mean by group		8.5/9.1
Mean, both groups		8.8

*The figure on the left of the slash is for mild effects (scored as 1), and the figure on the right of the slash is for marked effects (scored as 2).

**Potency ratio (1/ED50 of atropine ÷ 1/ED50 of second drug).

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Table A-V. Relative Central Potencies Based on Three Measures

Drug	Number facility	Behavior check list	Symptom check list	Mean
Atropine	1.0	1.0	1.0	1.0
Scopolamine (intramuscular)	7.5	7.5	8.8	7.9
Scopolamine (intravenous)	10.4	8.7	9.3	9.5
Ditran (intramuscular)	1.5	1.3	–	1.4

Table A-VI. Comparison of Central and Peripheral ED50's and Relative Potencies

Drug	ED50 (HR >30) μg/kg	Potency relative to atropine*	ED50 (NF <10%) μg/kg	Potency relative to atropine*	ED50 (NF <75%) μg/kg	Potency relative to atropine*	C/P ratio (NF <10%)	C/P ratio (NF <75%)	Steepness index **
Atropine	17.8	1.0	152.4	1.0	63.6	1.0	0.12	0.28	2.40
Ditran	86.4	0.2	100.0	1.5	54.0	1.2	0.86	1.60	1.85
Scopolamine (intramuscular)	23.1	0.8	20.2	5.0	9.4	6.8	1.14	2.46	2.15
Scopolamine (intravenous)	12.0	1.5	14.7	6.8	7.8	8.2	0.82	1.54	1.88
Methylscopolamine	5.0	3.6	-	-	16.7	3.8	-	0.30	-

* 1/ED50 of atropine ÷ 1/ED50 of second drug.
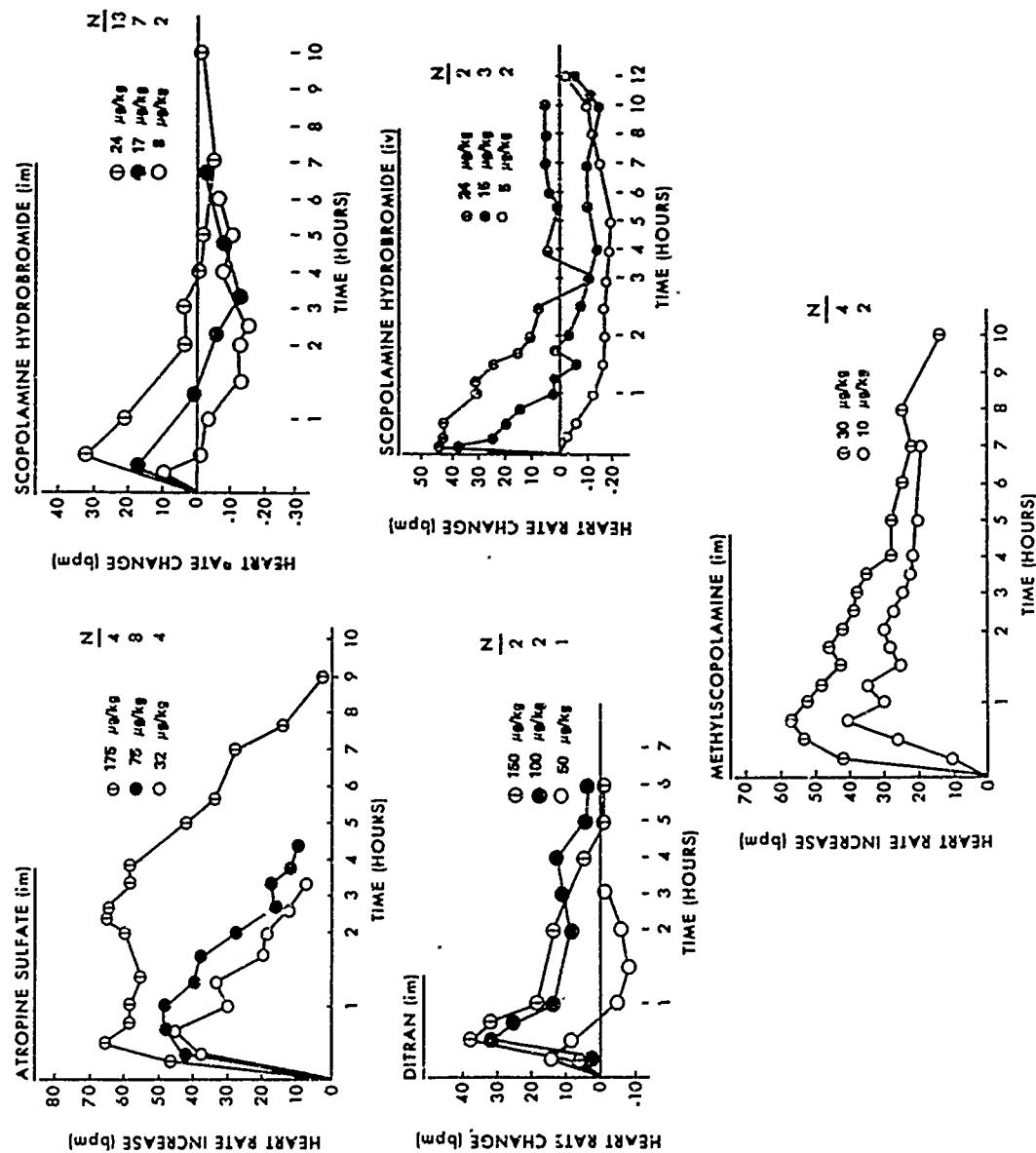** ED50 for NF <10% to ED50 for NF <75%.
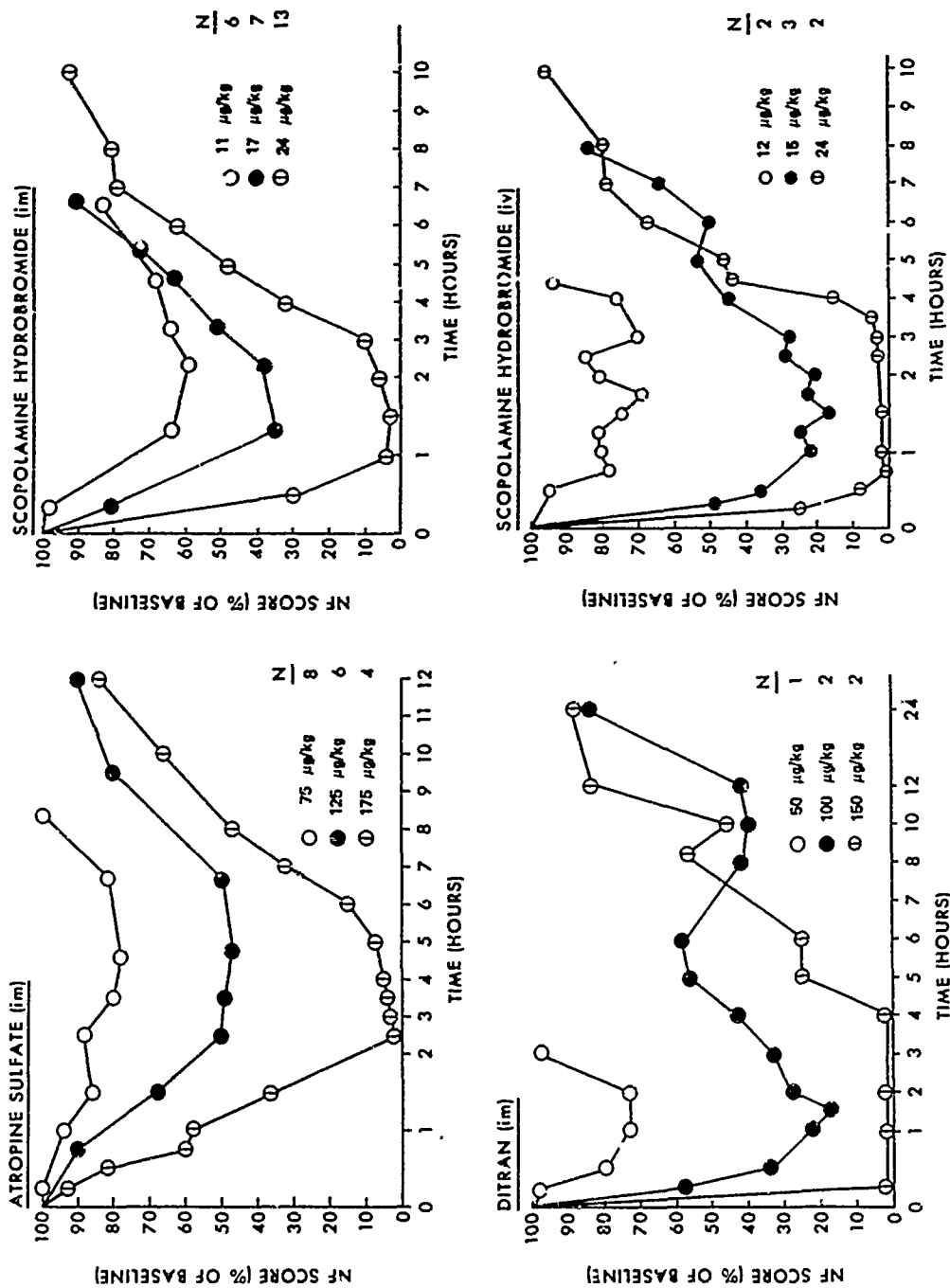
FIGURES

Figure B-1. Number Facility Scores Versus Time

The points are the mean values for the doses indicated. For clarity, not all dose groups are shown, nor are the standard deviations indicated.
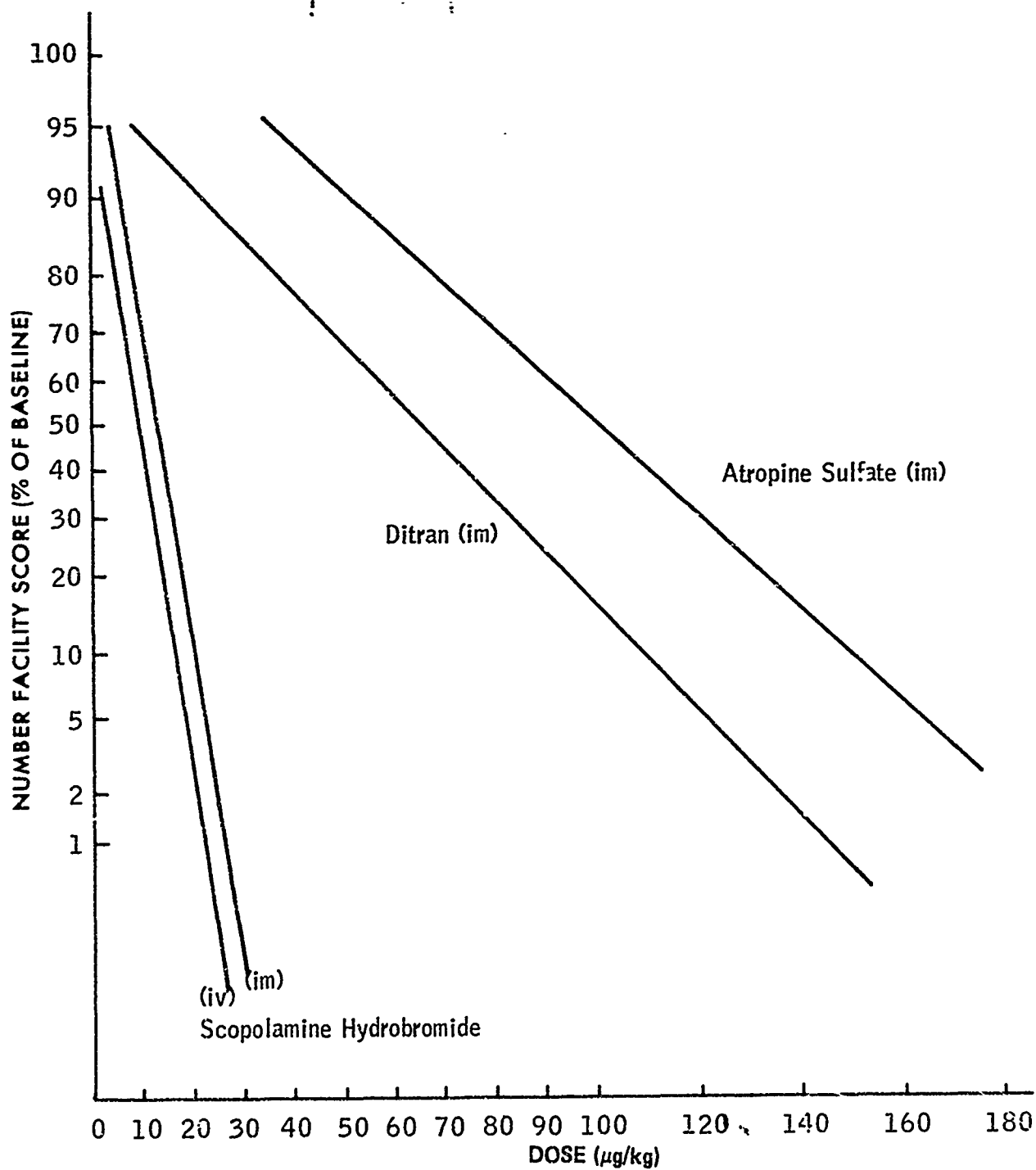
Figure B-2. Minimal NF Scores Versus Dose

In the regression analysis the minimal scores for all untreated
subjects were used. (See table A-I for the number in each group.)

DOSE (μg/kg)

SCOPOLAMINE HYDROBROMIDE (iv)   14.7

SCOPOLAMINE HYDROBROMIDE (im)   20.2

ATROPINE SULFATE (im)   152.4

DITRAN (im)   100.0

TIME OF DECREMENT GREATER THAN 50%

TIME OF DECREMENT GREATER THAN 75% (NF <25% OF BASELINE)

TIME (HOURS)

By probit analysis the ED50's for a 75% decrement in NF score (NF <25%) were estimated. Regression lines of dose versus the time for a given effect (e.g., dose versus time for a decrement greater than 50%) were calculated, and the times shown were calculated by inserting the ED50 into the appropriate regression equation.

Appendix B   33

Figure B-4. Mean Heart Rate Change Versus Time

The points are the mean values for the doses indicated. For clarity, not all dose groups are shown, nor are the standard deviations indicated.
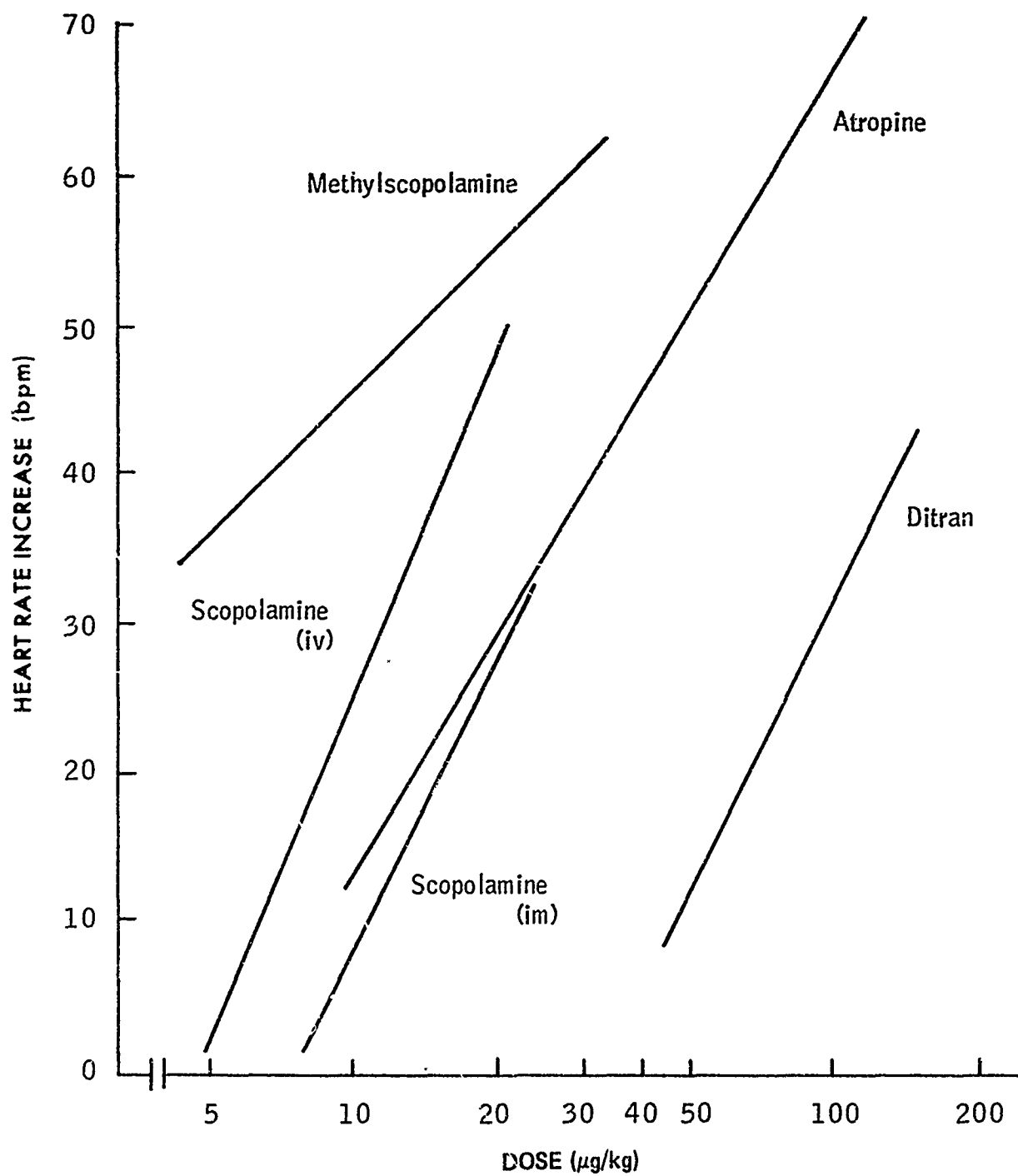
Figure B-5. Maximal Heart Rate Increases Versus Dose

Data from all untreated subjects were used in the
regression analysis. (See table A-I for numbers.)
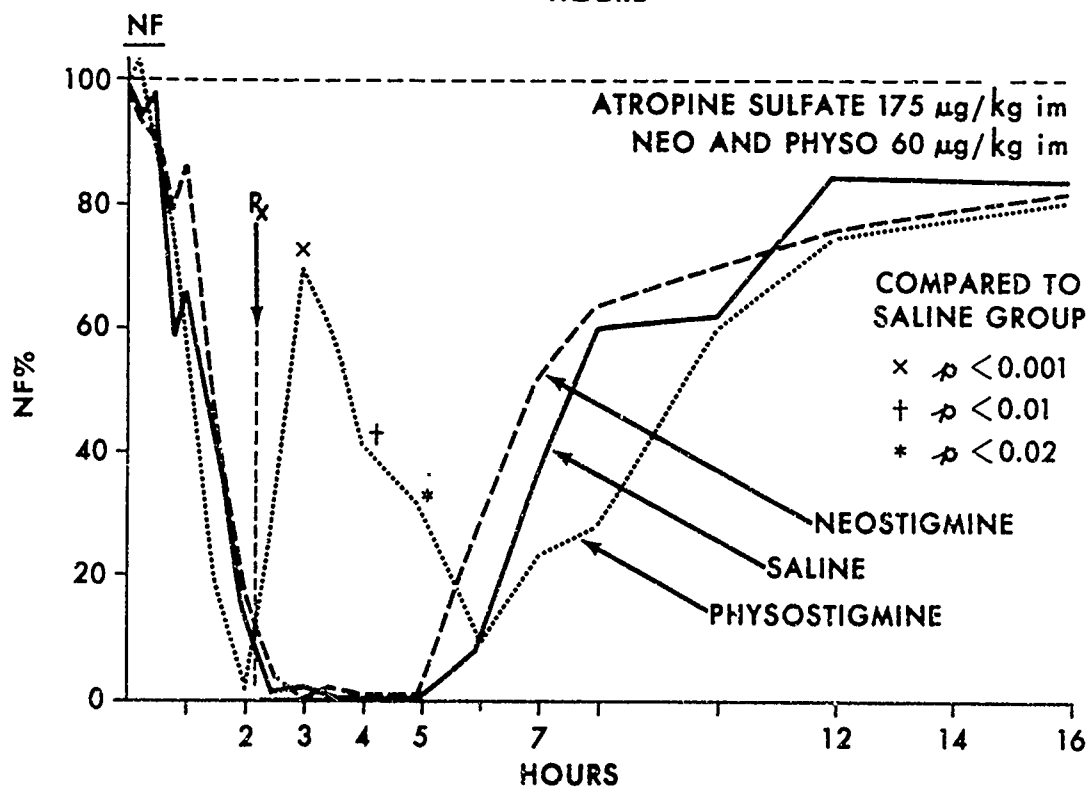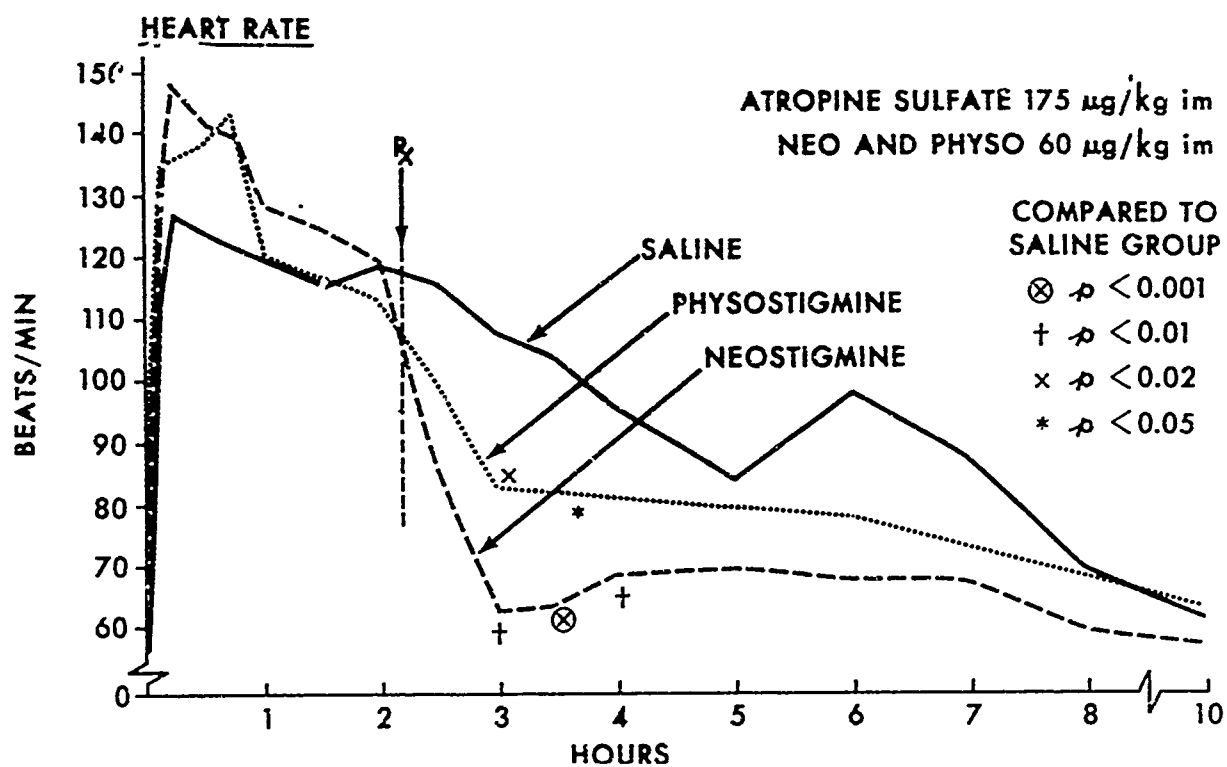
Figure B-6. Antagonism of the Central and Peripheral Effects
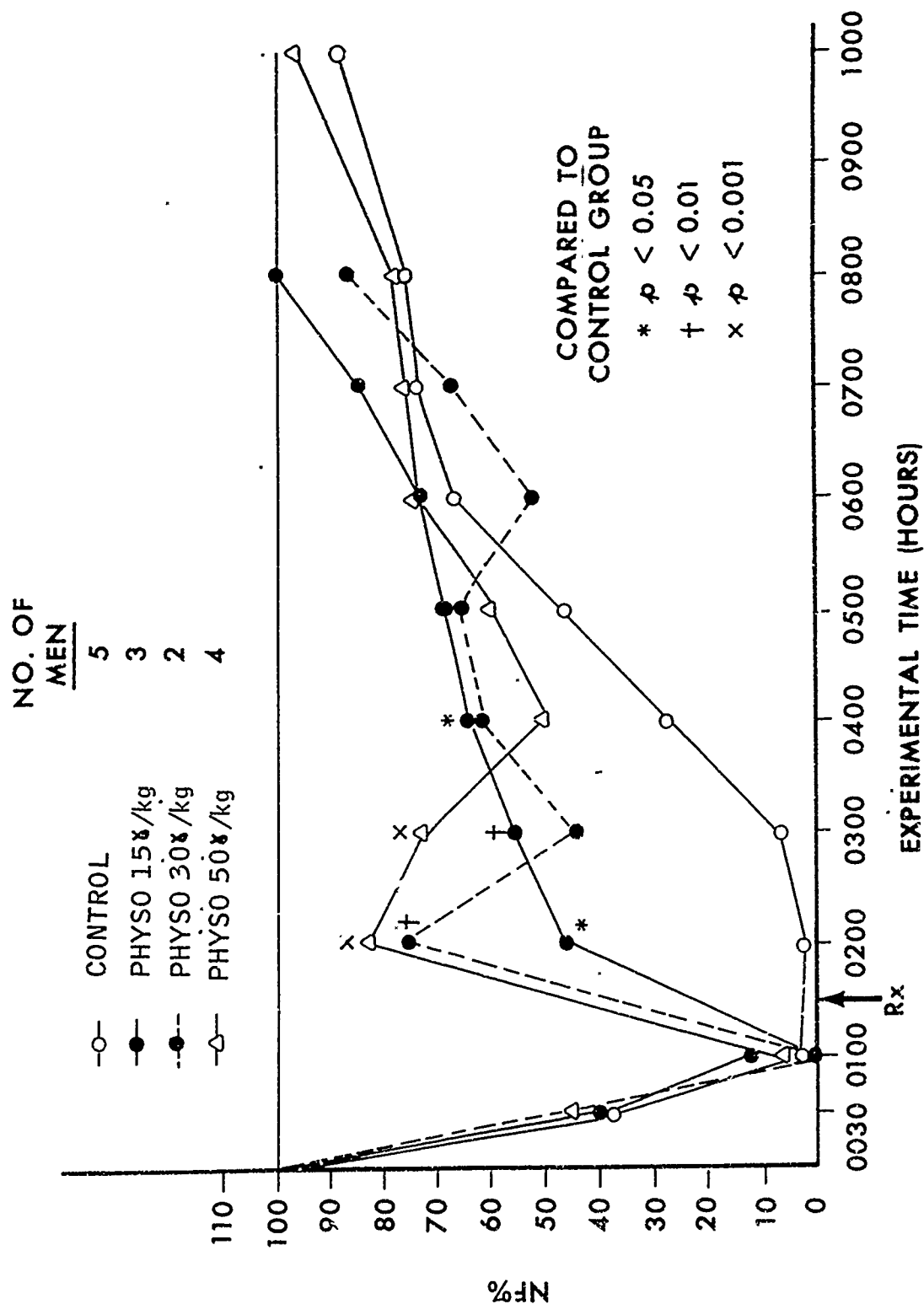of Atropine by Physostigmine, Neostigmine, and Saline

For each group N = 4.

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Figure B-7. The Effect of Different Doses of Physostigmine on its Therapeutic Effect in Scopolamine Intoxication
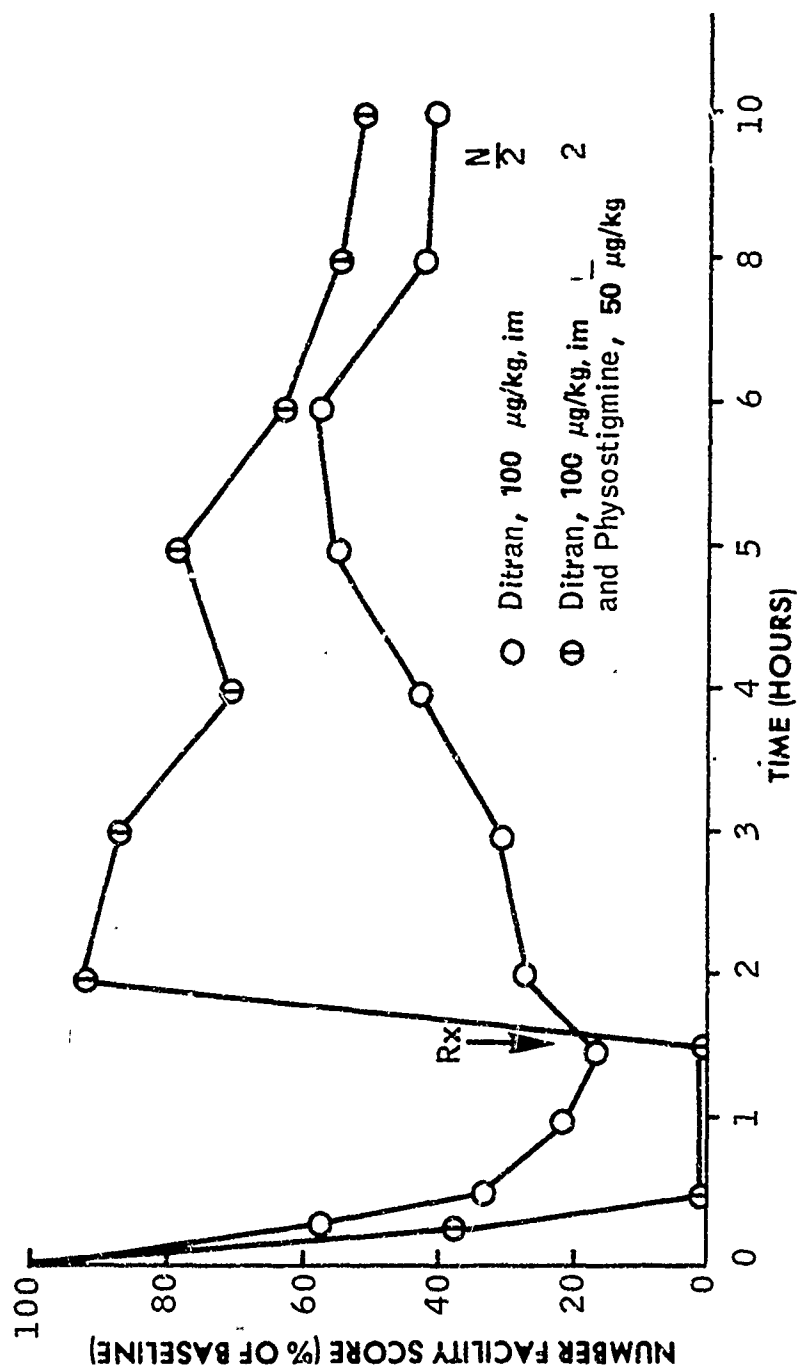
Figure B-8. Antagonism of the Central Effects of Ditran by Physostigmine

The heart rate response was similar to the response shown in figure B-6.
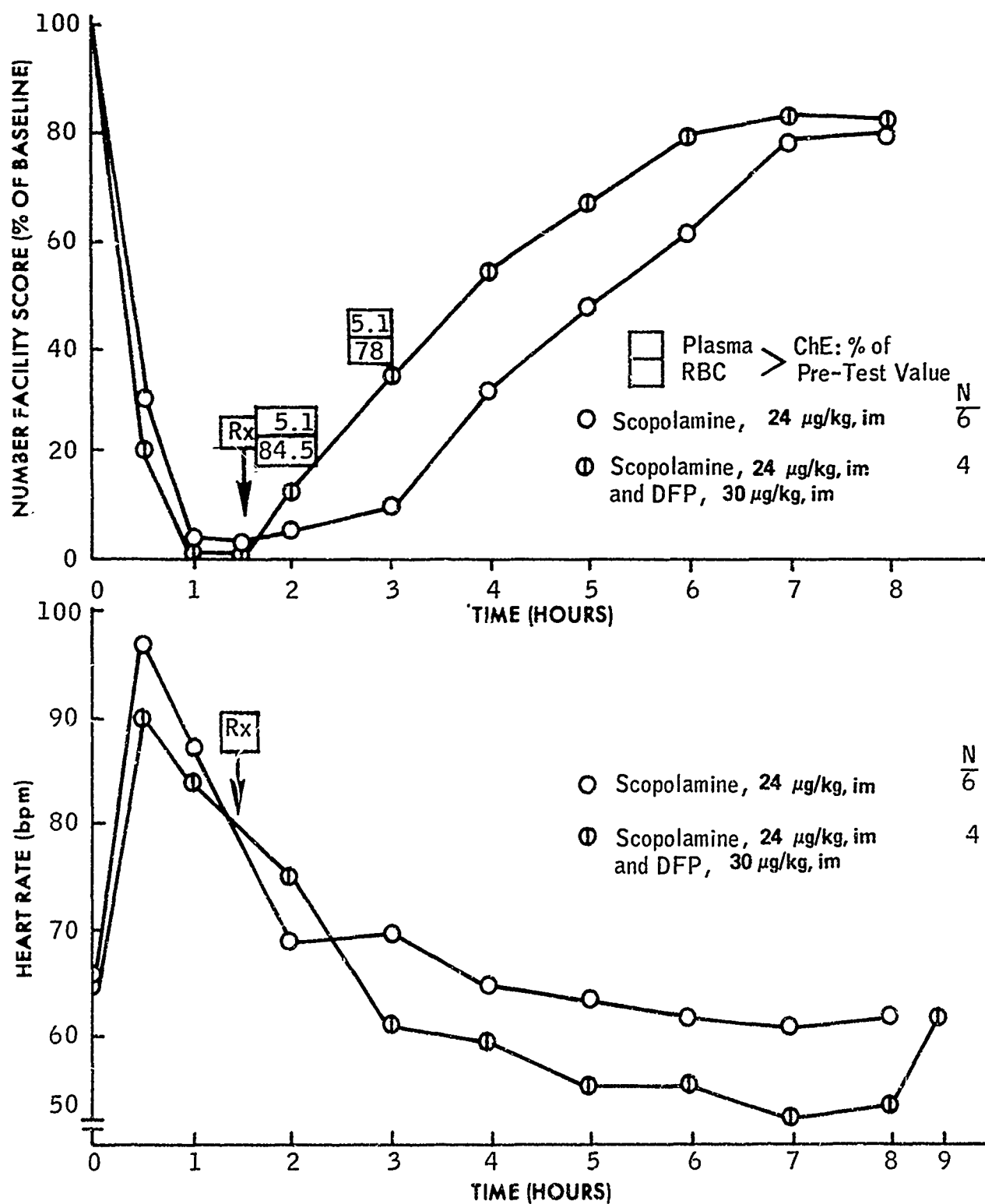
Figure B-9. Attempted Therapy of Scopolamine Intoxication by DFP

The improvement was minimal. Note the low plasma ("pseudo") cholinesterase and relatively high red blood cell ("true," acetyl) cholinesterase.
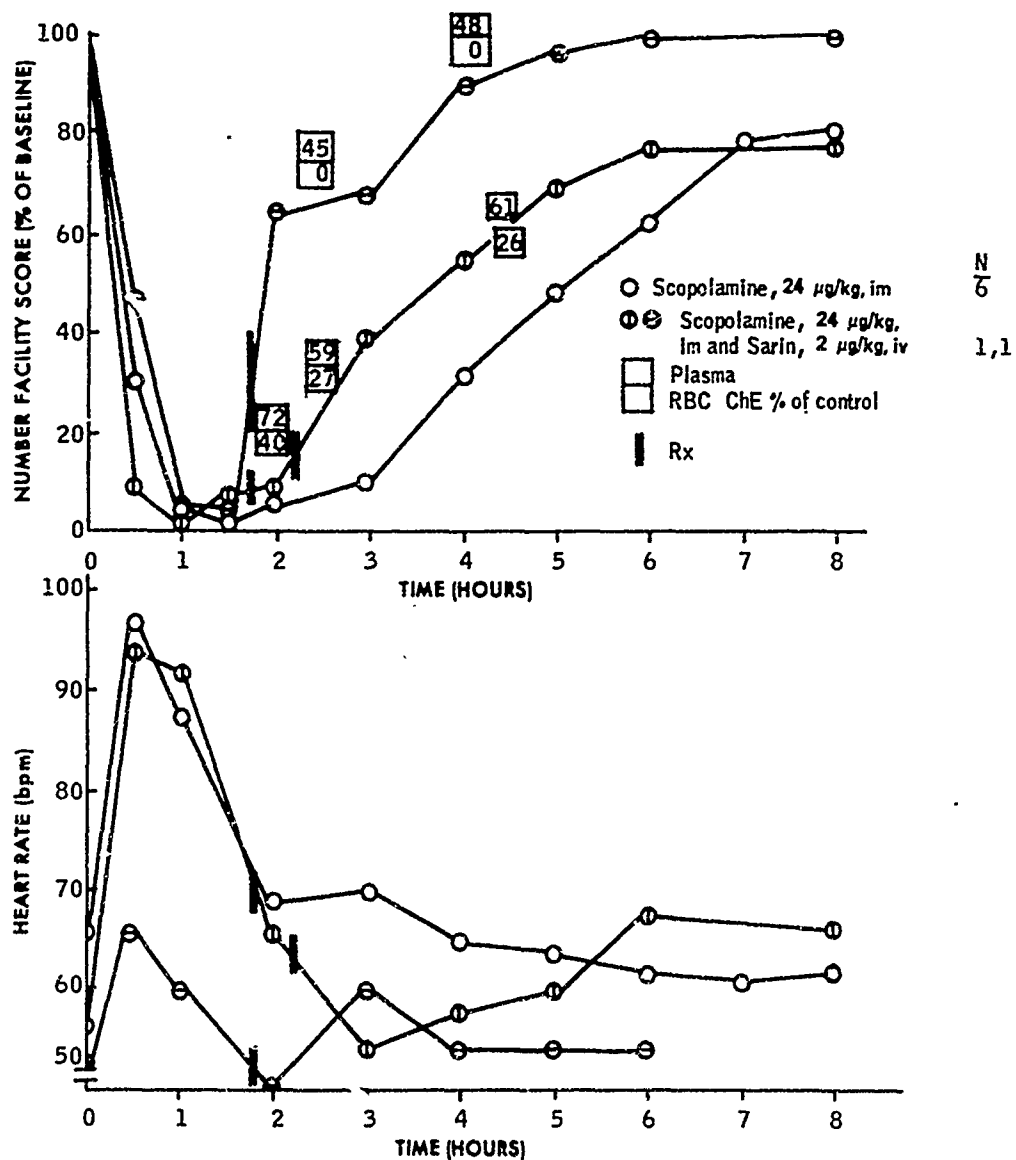
Figure B-10. Antagonism of the Central and Peripheral Effects
of Scopolamine by Sarin

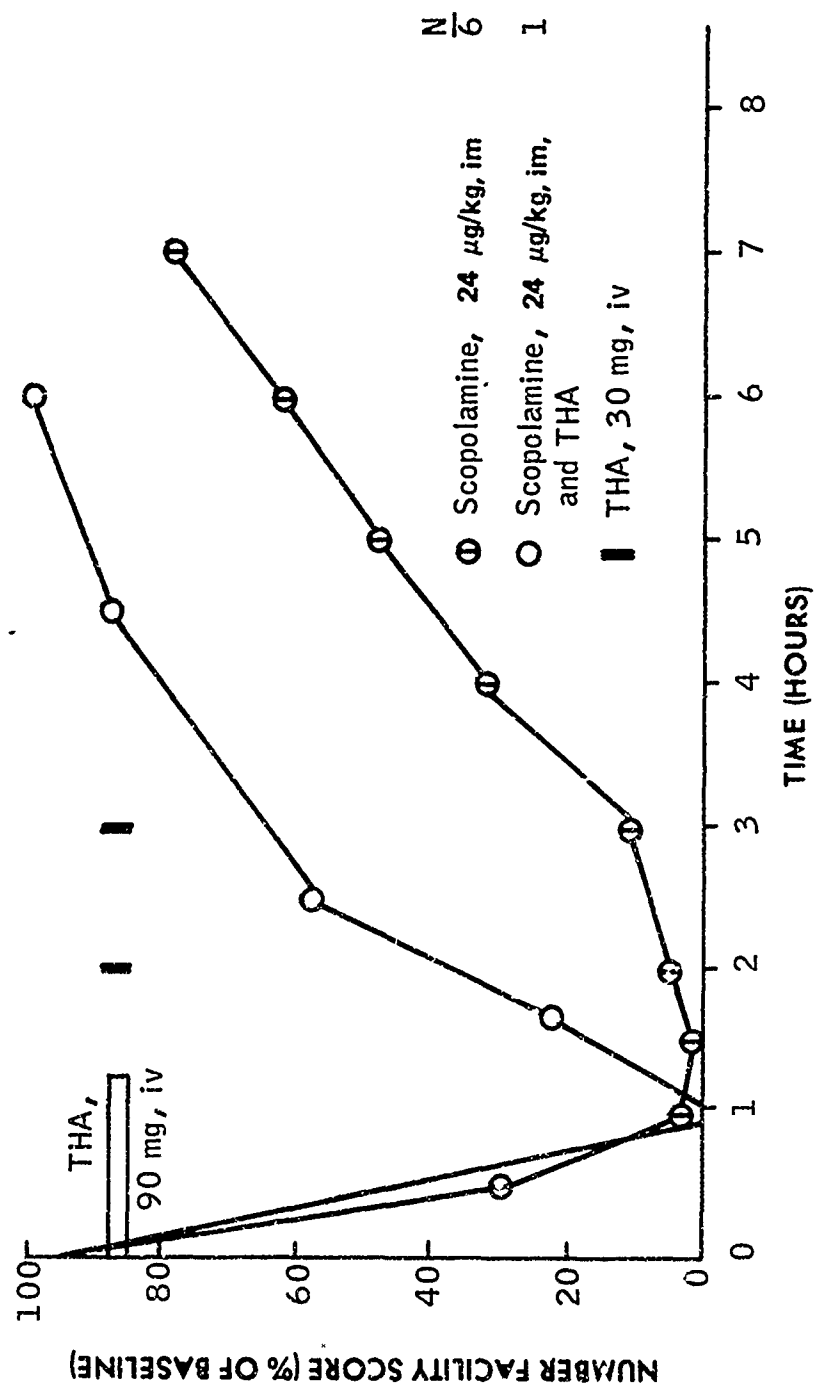Note the marked reductions in the red blood cell cholinesterase.

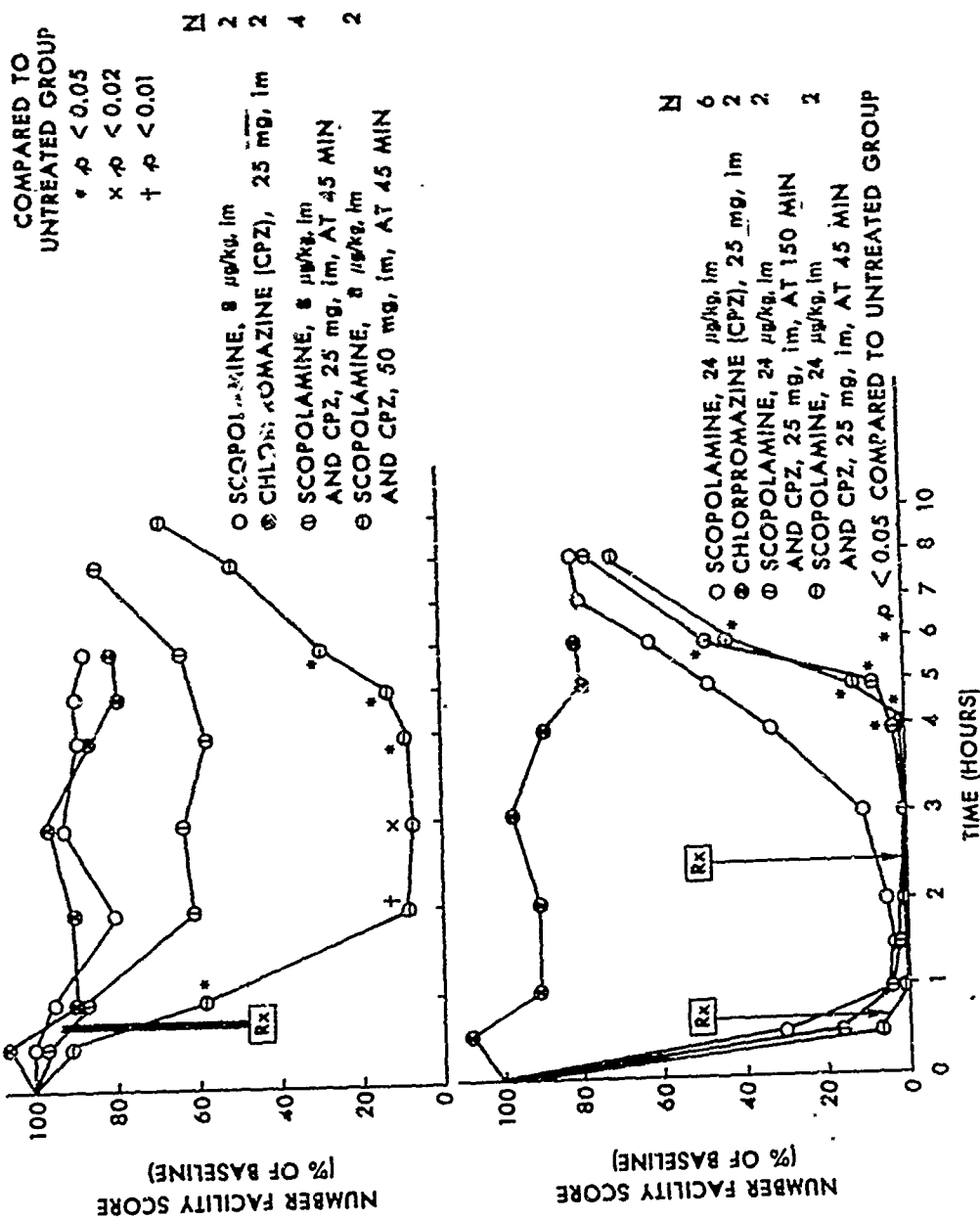Figure B-11. Antagonism of the Central Effects of Scopolamine by THA

Figure B-12. Potentiation of the Central Effects of Scopolamine by Chlorpromazine

Chlorpromazine alone (50 mg, not shown) produces a performance decrement only slightly greater than that produced by 25 mg.